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The rise and fall of breast cancer rates

Partly a result of trends in mammography screening and HRT use, but other factors must be considered

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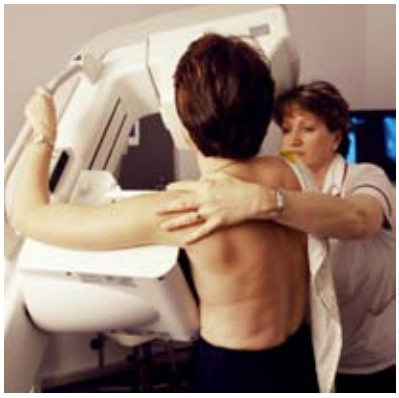
Around 2002, after several decades of steady increase, the incidence of breast cancer in many parts of the developed world began to decrease.[1 2] Several explanations for this decline have been proposed, but a favoured theory has been a reduction in the use of hormone replacement therapy (HRT) after release of the results of the Women's Health Initiative randomised trial.[1-4] In the linked study, Weedon-Fekjær and colleagues present ecological data supporting a role for mammography screening and HRT use in recent trends in the incidence of breast cancer.[5]

Ecological studies use aggregate data to explore correlations and time trends. No information is available on individuals, so no inferences can be drawn about cause and effect. Thus, Weedon-Fekjær and colleagues' study provides no data on whether the women who participated in the screening programme were the same women identified with breast cancer, or whether women who used HRT developed breast cancer more often than those who did not. Instead, the correlations reported are established by time trends within the population of Norway and by statistical modelling techniques. One of the shortcomings of aggregated data is the potential for erroneous conclusions—the introduction of screening programmes and increased acceptance of HRT use may have occurred at the same time as other changes that affected the incidence of breast cancer.

Whether the discrepant trends between [the USA and Norway] in the past few years are a modelling artefact or caused by factors beyond screening and hormone use will be the focus of studies in the years to come

Weedon-Fekjær and colleagues apply a method proposed in the mid-1980s to estimate the age group and calendar period specific incidence of breast cancer while simultaneously accounting for screening variables and HRT use on a population level.[6 7] They conclude that much of the rise and fall of breast cancer rates over the past two decades can be explained by the surge in incidence of breast cancer owing to the diagnosis of preclinical disease and (over)diagnosis of breast cancer by mammography screening between 1995 and 2004, and then the decline in breast cancer detection when women left the screening programme at age 69 years. A similar proportion of these trends can be accounted for by the increasing popularity in HRT until 2002, then the sharp decline in its use after the Women's Health Initiative was prematurely stopped.



MARK THOMAS/SPL

Mammography screening

Although it is reasonable to describe time trends in mammography screening, HRT use, and the incidence of breast cancer on the basis of data from the Norwegian population, the authors do not discuss artefacts that can arise in ecological data and age-period-cohort analyses when non-linearities are present—problems that were noticed only after the method was introduced. The basic problem is that such analyses are based on relations across group summary statistics, which are inevitably averages and cannot properly capture non-linearities and interactions correctly.[8 9] Thus, the authors claimed estimates of non-linear cohort and period effects must be at least partly distorted relative to the actual individual relations of breast cancer risk to HRT and screening; the degree of distortion can be assessed only with individual data.

In addition to these subtle modelling problems, several possible sources of confounding are unaccounted for. The time trends in mammography and HRT use were paralleled by changes in other factors in the same birth cohorts that may have contributed to the observed increase in breast cancer incidence trends—earlier onset of menarche, delayed child birth, lower number of children, and increasing weight gain after menopause. This problem and problems from non-linearities have no relation to goodness of fit of the model—the author's models could fit perfectly even if they were completely confounded or distorted by underlying non-linearities. Consequently, the estimated fraction of cases attributable to screening and HRT use is far more unreliable than the statistics make it appear (because those statistics account for random errors only, not biases). In particular, the authors' conclusion—that trends in breast cancer incidence since the early 1990s can be "fully attributed" to the introduction of mammography screening programmes and adoption of hormone treatment—cannot be justified on the basis of their data and analyses, because the data do not allow full adjustment for potential confounding variables and cannot properly reflect non-linearities and interactions.

This does not mean that the authors' conclusions are wrong, however, but that other evidence has to be considered too. Previous studies that have correlated time trends in breast cancer incidence with changes in screening and HRT use over time have also been based on population based estimates,[1-4] so individual level data are needed to evaluate the contribution of other factors.

Between 2004 and 2008, the incidence of breast cancer was steady in the United States,[10 11] consistent with a stabilisation in screening and hormone use. According to Weedon-Fekjær and colleagues' data, the incidence in Norway continues to decrease and, after accounting for trends in mammography and HRT use, continues to increase until 2008 (see fig 2, top panel, in Weedon-Fekjær and colleagues' paper).[5] Whether the discrepant trends between these countries in the past few years are a modelling artefact or caused by factors beyond screening and hormone use will be the focus of studies in the years to come.

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Because delirium is mostly hypoactive, where patients are quietly confused and apparently compliant, it remains underdiagnosed and underappreciated

Delirium in intensive care patients

Debate about assessment tools is overshadowing the importance of delirium

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The scientific evidence is irrefutable—delirium in the intensive care unit is an independent predictor of death and acquired dementia.[1 2] The linked study by Van den Boogaard and colleagues is the largest study on delirium in intensive care to date, and it provides a risk model to determine the likelihood of patients in intensive care developing delirium.[3] The model (PRE-DELIRIC), which determines 10 risk factors, was developed and validated at the Radboud University Nijmegem Medical Centre in the Netherlands. It was then externally validated at four other Dutch hospitals. The risk model showed a high predictive value, and it was significantly better than the predictions of doctors and nurses.

Reassuringly there are no surprises; risk factors that confer the highest risk are coma with any cause, sedatives, and infection. Notably there were too few patients with alcohol dependency or dementia for these subgroups to be included in the model. However, a prediction model is not needed to confirm that these patients have a high risk of delirium because alcohol dependency and cognitive impairment are significant risk factors in any clinical setting,[4] and both are non-modifiable.

Risk prediction models are increasingly influential. Once an effective risk model has been fully appraised and validated in the medical context in which it will be used, the next challenge is to implement it in practice. Having been successfully validated in intensive care, PRE-DELIRIC now faces that formidable task. An essential requirement for the model to be implemented is that critical care units are using computerised data input, but this is not the main barrier.

The problem is more fundamental—whether intensivists believe that delirium is important and whether sedated critically ill patients can be diagnosed as delirious. A survey in 2008 showed that only 18% of consultants in intensive care knew that delirium is associated with subsequent persistent cognitive impairment.[5] Although some intensivists might consider delirium in a patient with sepsis not important, all would recognise septic encephalopathy as so. Intensive care consultants recognise the importance of septic encephalopathy, but not that of delirium as the presenting symptom.

Intensive care is extreme medicine—consider fever in a medical patient as compared with severe sepsis in intensive care, or a clinic patient with an oxygen saturation of 93% as compared with hypoxia in a patient ventilated in intensive care. Delirium is common in intensive care—affecting 65% of sick ventilated patients in the United Kingdom[6]—and patients have multiple risk factors.[1] Because delirium is mostly hypoactive, where patients are quietly confused and apparently compliant, it remains underdiagnosed and underappreciated. This is infuriating for clinicians who see the devastating impact of delirium—over and above the effects of the illness for which they were admitted—on patients, their relatives, and friends.[7] Unless this problem is tackled, the implementation of risk prediction of delirium in intensive care will not progress.

In 1959, after seminal work that linked changes on electroencephalography to the alteration of consciousness in delirium, Engel and Romano bemoaned the fact that clinicians were more concerned with protecting the functional integrity of the heart, liver, and kidneys than that of the brain.[8] Why would clinicians neglect brain function? The degree of cognitive impairment is related to the duration of delirium, not to the number of days a patient spends on a ventilator.[2] Clinicians who consider delirium to be an epiphenomenon might ask whether renal failure is also an epiphenomenon.[9]

In 2001, two delirium screening tools were made available for intubated critically ill patients—the confusion assessment method for the intensive care unit (CAM-ICU) and the intensive care delirium screening checklist (ICDSC).[10 11] Both tools performed well against gold standard diagnosis using the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition. A positive CAM-ICU assessment or ICDSC score of 4 or higher is important because it is associated with increased mortality and cognitive impairment,[1 12] and it represents a robust clinical marker that needs attention.

One major difference between the tools is whether sedation confounds the diagnosis of inattention—reduced ability to focus, sustain attention, or shift attention—a core feature of delirium. Patients who are attentive do not have delirium. Intensive care clinicians often debate whether sedated patients can be diagnosed as delirious, but they are missing the point. Although screening tools have a place, it is not whether one is better or even valid; what matters for patients is for clinicians to recognise that they are delirious. Intensive care clinicians with a clinical understanding of the delirious state realise that patients who are thought to be depressed are actually delirious, as are apathetic immobile patients, who were previously thought to be still recovering from sedation.

Without a diagnosis of delirium, the precipitating cause cannot be identified or treated. By failing to identify patients at high risk, the opportunity to prevent delirium by modifying predisposing risk factors, as recommended by the National Institute for Health and Clinical Excellence, is lost.[13] Research into delirium in the clinical setting needs to move from observation to intervention to identify drugs that can prevent or modify delirium and improve outcomes. Hopefully, such studies would answer the question of whether high risk patients and hypoactive delirious patients need to be treated with antipsychotics. Finally unless it is known that one type of delirium, such as sedation induced delirium, is less serious than another, such as septic induced delirium, clinicians must look for delirium in every patient using whatever means they have confidence in and decide at the very least "is there anything I can do to treat the cause?"

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- Newer drugs for focal epilepsy in adults (*BMJ* 2012;344:e345)
- Juvenile myoclonic epilepsy (*BMJ* 2012;344:e360)

Sudden death in epilepsy

Optimum seizure control and prompt referral to specialist services are essential

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People with epilepsy have a higher risk of premature death throughout the course of the condition.[1 2] One of the most important causes of mortality is sudden unexpected death in epilepsy (SUDEP), defined as "sudden, unexpected, non-traumatic, and non-drowning death in patients with epilepsy, with or without evidence for a seizure, and excluding documented status epilepticus, in which postmortem examination does not reveal a structural or toxicological cause for death."[3] In practice, all such deaths where an autopsy is performed are classified as definite SUDEP and those in which no autopsy is performed as probable SUDEP.

SUDEP is the most common epilepsy related cause of death in people with chronic epilepsy. Its incidence varies greatly depending on the population studied and the methods used, with a clear increase as the severity of epilepsy increases. Incidence ranges from less than 1 per 1000 person years in people with epilepsy in community based studies, to 2-5 per 1000 person years in people attending tertiary specialist clinics, and 6-9 per 1000 person years in candidates for epilepsy surgery.[4 5] Overall, young adults with epilepsy are almost 24 times more likely to die suddenly than members of the general population.[5] In the United Kingdom, SUDEP is estimated to kill more than 500 people a year.[6]

In an effort to identify risk factors, a recent study pooled and analysed data from four large SUDEP case-control series.[7] The profile of a person at increased risk of SUDEP was male (odds ratio 1.4), with a younger age of onset (<16 years; 1.7), and a longer duration of epilepsy (duration >15 years; 1.95). One of the most important risk factors identified was the frequency of convulsive seizures. People with these seizures were at higher risk than people without them, with the risk increasing with the frequency of convulsive seizures each year (compared with no convulsive seizures, one to two seizures, odds ratio 5.1; three or more seizures, 15.5). Polytherapy with antiepileptic drugs alone (odds ratio 1.95) or in association with increasing frequency of seizures (three or more seizures and polytherapy; 22.6) was also an important risk factor, although this may simply reflect the severity of epilepsy.[7]


CHAGNON/SPL

Emergency team treats epileptic seizure patient

Most cases are unwitnessed. The person is often found dead in (or by) the bed and there is usually evidence of a recent convulsive seizure. In witnessed cases, there are often reports of difficulty in breathing before death.[8] Studies examining the mechanisms underlying SUDEP have focused on possible seizure related or drug induced cardiac arrhythmia, respiratory dysfunction including central respiratory hypoventilation, dysregulation of the cerebral circulation, seizure induced cessation of brain activity, and seizure induced hormonal and metabolic changes. It is likely, however, that SUDEP is triggered by a combination of seizure related predisposing and precipitating factors rather than a single factor.[4 9]

The increased premature mortality in people with epilepsy and its possible prevention was highlighted in a recent case-control study, partially funded by Epilepsy Bereaved, a UK based non-governmental organisation that has worked to raise the profile of epilepsy related death, particularly SUDEP. Using data from the general practice research database, it found that failure to collect repeat prescriptions for antiepileptic drugs was an important risk factor.[10] In another study, poor adherence with drug treatment was associated with increased mortality (of which some deaths were undoubtedly SUDEP).[11]

In the UK National Clinical Sentinel Audit of Epilepsy-related Death,[6] 60% of deaths were classified as probable SUDEP and 7% as possible SUDEP. In adults, about a third of deaths were thought to have been potentially avoidable (they were mainly caused by lack of access to specialist services or inadequate treatment), and a further 9% were probably avoidable. In children the figures were more stark, with 55% potentially or probably avoidable.[6]

The US National Institutes of Health recently sponsored a workshop dedicated to SUDEP. Several recommendations were made, including increasing awareness, establishing collaborations between support groups, developing a SUDEP practice guideline, and focusing research on modifiable risk factors.[12]

The precise pathophysiological mechanisms underlying SUDEP are uncertain so any proposed measures to reduce the risk are speculative. It is important to raise awareness, particularly among family doctors, because potential methods to reduce the risk include attaining full control of seizures, ensuring timely repeat of antiepileptic drug prescriptions, encouraging good antiepileptic drug adherence, and ensuring early and prompt referral to specialist services.[4 9 10 12] Other measures such as night-time supervision and the use of alarms in people at high risk (such as those with severe refractory epilepsy or learning disability) seem to be important in preventing SUDEP.[8] Similarly, all healthcare professionals and carers of people with epilepsy should be counselled about the importance of continuous supervision after a convulsive seizure until full consciousness returns.[4]

Nevertheless, some people with epilepsy will still die suddenly, sometimes early in the course of the condition and sometimes in the context of previously well controlled epilepsy. In all cases, doctors must contact the family and others concerned to offer sympathy and support. Relatives and friends should also be made aware of the existence of charities such as Epilepsy Bereaved (www.sudep.org), so that all involved can receive appropriate counselling.

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- *BMJ* blog: Nick Foreman on road safety http://blogs.bmj.com/bmj/2010/06/24/nick-foreman-on-road-safety/
- Personal view: It could happen to anybody: why 20 mph speed limits matter (*BMJ* 2010;340:c2813)

Proposals to increase the motorway speed limit by 10 mph

Any potential economic benefit is likely to be outweighed by the adverse effects on health

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By 2013 the speed limit on motorways in England and Wales could increase from 70 mph (113 kph) to 80 mph if the coalition government has its way. Its stated aim is to achieve "hundreds of millions of pounds of benefits for the economy," and it dismisses concerns about health consequences, claiming that advances in car safety have resulted in deaths on British roads falling by more than 75% in the past 55 years and that almost half of all drivers break the current limit anyway.[1] Are they right to dismiss these concerns so lightly?

PAUL WHITE/TRANSPORT INFRASTRUCTURES/ALAMY

The current 70 mph speed limit was trialled in 1965 as a direct response to a series of fatal multiple collisions in fog. Before then speed was unrestricted outside built-up areas. By 1967 the Road Research Laboratory concluded that this restriction had led to a reduction in road fatalities,[2] and Barbara Castle—then minister of transport—made it permanent. Since then the number of serious and fatal accidents has continued to fall and the United Kingdom now has one of the lowest rates of road deaths worldwide.[3 4] Elsewhere, speed limits vary from 55 mph on the freeways in some parts of the United States to no upper limit on large parts of the autobahns in Germany.

It is intuitive that higher speeds will result in more collisions and that collisions at such speeds are likely to result in more serious injuries and deaths, a perception supported by the evidence. Research in several countries including the UK has shown an exponential increase in the number of crashes involving injuries and deaths with higher speed.[5-8] However, the health consequences extend beyond road safety. They include greater emissions and consequent air pollution, and, potentially, rising levels of obesity as a result of increased car use among those taking advantage of shorter journey times.[9 10]

The crucial question, however, is what happens when speed limits change. Several natural experiments in the past 20 years can provide insights. In general, where speed limits have been reduced, injuries and fatal crashes have decreased; conversely where speed limitshave been increased, the number of deaths has risen substantially.[5 8] The example that is arguably the most comparable to the UK proposal was the increase in speed limits in many US states after 1995 when the national maximum speed limit, introduced in response to the 1974 oil crisis, was repealed—limits on interstate highways and freeways were increased, typically from 65 mph to 70-75 mph or from 55 mph to 60-65 mph. This was associated with a 16.6% increase in deaths.[11] However, a higher speed limit may persuade more people to use their cars rather than other forms of transport, so the increase in deaths may reflect both greater traffic volumes and increased collision risk. Of course, as the government rightly notes, many people already drive above the speed limit, but it is difficult to believe that they will resist the temptation to continue to exceed a higher limit. On this evidence, the government's dismissal of adverse health effects seems, to say the least, shaky.

Neither is it clear where it obtained evidence for the alleged economic benefits of its proposal. Heavy goods vehicles would still be limited to 60 mph, and because most work related driving in smaller vehicles takes place during the busiest periods, when roads are already overcrowded, it is difficult to see how journey times will be greatly reduced. The anticipated rise in collisions may itself slow traffic. Potential negative economic effects must also be considered, such as those set out in the government's own valuation of road accidents and casualties,[3] not least of which are increased healthcare costs and depletion of labour supply from those killed and injured. Indeed, given that the incidence of road traffic injuries is highest among those of working age, these adverse economic consequences may be considerable.[5]

If the government was serious about achieving economic benefits it would consider investing in alternatives with a less negative health impact, such as public transport. Examples include extending coach and bus lanes on motorways during busy periods or subsidising rail fares, rather than the planned increases in the cost of travelling on the trains that the transport secretary has described as "a rich man's toy."[12]

In the light of this evidence, it is difficult to see the proposal to raise the speed limit as anything other than a populist gimmick, albeit one that may now be less popular after the recent tragic loss of life on the M5 motorway.[13] Given the clear negative public health and environmental effects, the government must show substantial countervailing economic benefits that cannot be achieved in other ways. This may be quite a challenge.

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